Food and Drug Administration
OFFICE OF CRIMINAL INVESTIGATIONS
REPORT OF INVESTIGATION

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CASE TITLE:	AVENTIS PHARMACEUTICALS, INC. - KETEK
CASE AGENT:	DOUGLAS LOVELAND
INVESTIGATION MADE AT	Multiple; See Text
INVESTIGATION MADE BY	Douglas M. Loveland
REPORTING PERIOD	**FROM:** 02/27/2007 **TO:** 04/24/2007
STATUS OF CASE:	Continued.
SYNOPSIS:	Regulatory Background of NDA 21-144; Identifying Falsified Data in Study #3014 and AVENTIS' statements in defense of its submissions

REPORT SUBMITTED BY _____ DATE: 04/24/2007
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REPORT APPROVED BY: _____ DATE:
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1. INTRODUCTION:

This investigation was opened on 03/09/06 after AVENTIS PHARMACEUTICALS, INC. (hereinafter, "AVENTIS") submitted falsified data in a new drug application (NDA). This is the fifth ROI in this investigation.

On 02/28/00, AVENTIS filed NDA # 21-144 seeking approval of Ketek (telithromycin), the first antibiotic of the ketolide class, for various respiratory infections. Concerned about hepatotoxicity signals in reported Phase I and Phase III trials, and after seeking guidance from an advisory committee, FDA suggested AVENTIS conduct a phase III study to further assess adverse events associated with telithromycin.

AVENTIS conducted Study # 3014 from 10/19/01 to 05/14/02, enrolling, treating and analyzing the results from 24,137 patients at 1824 sites. In its final study report submitted to FDA 71 days later, AVENTIS represented that the trial had been conducted to good clinical practice (GCP) standards. Subsequent inspections by FDA's Division of Scientific Investigation (DSI) demonstrated that much of the data produced by the highest enrolling, most intensely monitored and audited sites were unreliable. DSI concluded that the integrity of the entire trial data could not be assured. An OCI investigation of the highest enrolling clinical investigator revealed that data from approximately 91% of her patients were falsified. Despite warnings by its own contract research organization (CRO), AVENTIS included all of the site's data in its study submission to the FDA in July 2002 and in a subsequent presentation before a second advisory committee meeting in January 2003.

FDA asked AVENTIS to convince the agency the study data were reliable and submit foreign post-marketing data from Europe and South America, where the drug had been approved since 2001. AVENTIS did both, but FDA remained uncertain of the data's integrity. Eventually relying entirely upon foreign post-marketing data and clinical trials other than Study #3014, FDA approved Ketek on 04/01/04.

2. DETAILS OF INVESTIGATION:

According to financial reporting and an FDA establishment inspection conducted in May 2006, Sanofi-Synthelabo completed its acquisition of AVENTIS SA, the French parent firm of AVENTIS, in August 2004. Sanofi-Synthelabo immediately changed its name to SANOFI-AVENTIS (Attachment 1). A review of the Security and Exchange Commission's (SEC's) EDGAR database disclosed that AVENTIS terminated its registration with the SEC on 01/03/05 (Attachment 2).

The official website of the State of Delaware, Office of the Secretary of State, Division of Corporations, listed only two corporations identifiable as "Aventis Pharmaceuticals, Inc." chartered in the state of Delaware. The first was incorporated as a corporation on 07/09/64 under file number 0613109. The second was incorporated as a corporation on 10/08/65 under file number 0631221. Neither corporation's current status was available online (Attachment 3).

The official website of the State of Delaware, Office of the Secretary of State, Division of Corporations, listed two corporations identifiable as "Sanofi-Aventis" chartered in the state of Delaware. The first, Sanofi-Aventis U.S., LLC., was incorporated as a limited liability company on 07/25/00 under file number 326446. The second, Sanofi-Aventis U.S., Inc., was incorporated as a corporation on 12/17/03 under file number 3741501. Both dates precede the FDA's approval of Ketek. Neither corporation's current status was available online (Attachment 4).

During this reporting period, electronic access was gained to NDA #21-144, the files of the Anti-Infective Drug Advisory Committee (AIDAC) and OCI file number 2003-NEL-707-0040-J regarding

Anne Kirkman-Campbell. These sources disclosed that FDA approved the Ketek application after AVENTIS made three separate, complete NDA submissions. As is detailed below, the first submission was insufficient because of the relatively small number of patients exposed to telithromycin and the inadequate explanation of the hepatotoxicity signal seen in Phase III trials. The second major submission became hamstrung by a large safety study in which the FDA placed little confidence. The third application contained a great deal of post-marketing data from 36 countries and it was this third submission that FDA approved to market Ketek in April 2004. It was also the only submission to report a myasthenia gravis exacerbation signal, the adverse event that led to a black-box warning on Ketek's label in February 2007.

THE FIRST SUBMISSION

On 2/28/00 and as modified in subsequent correspondence, AVENTIS submitted the original NDA #21-144 for Ketek in four indications: community acquired pneumonia (CAP); acute sinusitis (AS); acute exacerbation of chronic bronchitis (AECB) and tonsillopharyngitis (T/P). After reviewing the application, the FDA's Division of Anti-Infective Drug Products (DAIDP) expressed concern regarding Ketek's safety profile (particularly with respect to cardiac effects and hepatotoxicity) and its resistance claims for S. pneumoniae. DAIDP separated out the T/P indication into a separate NDA and then asked the Anti-Infective Drug Advisory Committee (AIDAC) to render an opinion concerning the remaining three indications, focusing on Ketek's risk-benefit ratio (Attachment 5).

On 4/26/01, the AIDAC met to consider Ketek's application. The meeting transcripts show the panel heard a presentation on drug-induced Q-T interval prolongation, a cardiac conduction defect unique to some drugs and which was suspected in this drug. Q-T interval prolongation infrequently induces Torsades de Pointes, a potentially lethal cardiac dysrhythmia. Several representatives from AVENTIS then gave presentations, primarily concerning Ketek's efficacy in the sought-after indications. In the afternoon session, two FDA physicians and a liver toxicity expert from the Armed Forces Institute of Pathology (AFIP) gave the committee information concerning hepatotoxicity issues surrounding the drug.

In summarizing the studies cited in AVENTIS' application, FDA officials described to the committee how in the firm's Phase I trials, patients tended to experience a noted increase in some transaminases in a dose-dependent relationship. In both controlled and uncontrolled Phase III trials, a total of 3265 patients received Ketek and there were three cases of hepatitis reported. Only one patient's liver was biopsied, and the microscopic examination of the biopsy at AFIP revealed that the cellular necrosis was similar in location, scope and form to necrosis found in the livers of patients experiencing drug induced hepatitis secondary to Trovan use. (AGENT'S NOTE: The antibiotic Trovan was removed from the marketplace following findings of liver toxicity.)

The AIDAC's discussion then revolved around risk v. benefit ratios, and whether the data presented provided enough information for the committee to recommend to the FDA that the drug should be approved for its proposed indications. The general consensus was that there was insufficient data presented, either with respect to efficacy in certain indications, or with respect to hepatic and cardiac safety concerns, or both, to make meaningful recommendations. The committee then contemplated advising the FDA to mandate various drug use restrictions, registries, black-box warnings or other limitations if the drug was approved.

Finally, Dr. L. Barth Reller, Chairman of the AIDAC, stated, "I favor finding out more about the drug up front, to possibly minimize all of the boxes and warnings after the fact... Now, I realize that if it's an event that's one in a million, it's impractical. But once widely available, I mean the potential market is in the millions; so as a consequence, I'd like to see a lot more than 1,500 - 2,000 patients. And it's not an

issue of demonstrating efficacy anymore; it's an issue of focusing on those things that might give a good indication of community acquired pneumonia." Other committee members agreed, and the committee's eventual recommendation was that the drug might be approved only for the indication of community acquired pneumonia, but further prospective investigation involving a large number of patients would help clarify or alleviate the committee's concerns about Q-T prolongation and liver toxicity and their relationship to expected benefit. A copy of the advisory committee meeting minutes, which document the votes and the recommendation, is appended at Attachment 6.

On 06/01/01, FDA issued an "approvable letter" to AVENTIS, which stated the application was approvable with respect to three of the four requested indications. The letter requested AVENTIS conduct two specific investigations and gave feedback on data AVENTIS had already submitted. FDA further stated, "It would be helpful to conduct a phase III study of CAP/ABECB/ABS to assess further adverse events associated with telithromycin, particularly in patients at increased risk for potential drug-related toxicity" (Attachment 7).

STUDY #3014

During the period of 6/1/01 through 10/18/01, AVENTIS and FDA communicated on several occasions regarding the design and construct of a phase III trial, which AVENTIS subsequently named "Study #3014." According to the Clinical Trial Protocol (Attachment 8), AVENTIS and FDA agreed upon a large, simple safety study (LSSS) as the final design, which called for a comparative, randomized 1:1, open-label, multicenter study of 24,000 patients. Half the study population would receive telithromycin and the other half would receive Augmentin, a comparator antibiotic. The design further called for a risk enriched, CAP-oriented population, with about a third of all patients being in excess of 50 years old. The study was intentionally powered to detect adverse events at a ratio of one or more per four thousand patients with a very high degree of confidence, which is why 12,000 patients were to be randomized to the telithromycin arm (See: Attachment 8, pg. 36).

The study was to be conducted to GCP standards as identified in ICH E6 Good Clinical Practice (See: Attachment 8, pg. 37), which has been adopted by FDA as Guidance for Industry and published in the Federal Register at 62 FR 25692.

(AGENT'S NOTE: ICH E6 Good Clinical Practice, at Section 5.20, states as follows: "5.20.1 Noncompliance with protocol, SOPs, GCP and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance. 5.20.2 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should promptly notify the regulatory authority(ies)" (ICH E6 GCP Guidance, cover and pg 37, Attachment 9).)

AVENTIS conducted Study # 3014 during the period of 10/19/01 through 05/14/02, enrolling 24,562 patients at 1824 sites in the US. Of those patients, 139 patients were not randomized; 33 patients were randomized to the wrong drug; nine patients were randomized but no data were collected; 284 patients were randomized but not treated, and no post-baseline data was available for three patients. Thus, the actual number of patients analyzed (referred to as "safety evaluable" patients) was 24,137, and this number became the final number of patients in the trial (Attachment 10). Nadine Grethe was AVENTIS' study manager; William Stager, PhD, was the study's biostatistician; Roomi Nusrat, MD, was clinical study director, and Professional Pharmaceutical Development, Inc. (hereinafter, "PPD") was the CRO. PPD was responsible for recruiting, training and monitoring clinical investigators during the

course of the trial. AVENTIS QA personnel, including Gerard Marini, then Head of GCP NA Operations Center; Michael Shoemaker, R.PH., PhD, Head of Quality Assurance; and Ranjan Khosla, MD, Senior GCP QA Specialist, oversaw quality assurance issues. Khosla also conducted audits on behalf of AVENTIS.

During the course of the trial, AVENTIS QA and its CRO detected problems and protocol violations which were significant enough to potentially affect the integrity of data at a minimum of eleven sites, identified as follows:

1. Site # 1124, Dr. Ankur Sarkar

Sarkar enrolled nine patients, though it was a breach of his contract with the hospital that owned the clinic in which he worked. Repeated telephonic and in-person monitoring events failed to produce completed study forms, such as informed consents, case report forms or other standard documentation. AVENTIS terminated Sarkar's participation in the study and excluded eight of Sarkar's nine enrolled patients from its study analysis (Attachment 11, pg 1; see also Clinical Study Report Table 2, pages 214-257, voluminous and not attached).

2. Site # 2340, Dr. Richard Barber

Barber enrolled two patients and randomized one to a study medication. However, when PPD discovered the patient had an allergy to penicillin (a study exclusion), Barber terminated his participation in the study and refused to communicate with PPD or AVENTIS. After nine phone calls and an attempted on-site monitoring visit (in which Barber refused to participate) the one patient's data was excluded from the study analysis and the FDA was notified (Attachment 11, pgs 2-3). AVENTS' 7/24/02 submission of the study to FDA showed no patients were enrolled, randomized or identified as safety evaluable from this site (Clinical Study Report Table 2, pages 214-257, not attached).

3. Site # 0024, Dr. Jay Franklin

Franklin, a pediatrician in Miami, FL, enrolled 16 patients into Study 3014. Some were underage, others were parents of his pediatric patients but upon whom no source records or medical charts were kept. Franklin appeared on a spreadsheet entitled "Low AE Reporting" with the annotation that none of the adverse events could be verified because of the lack of source records (Attachment 12). Nonetheless, Franklin's data was included in the final study analysis (Clinical Study Report Table 2, pages 214-257, not attached).

4. Site # 0469, Dr. Vincent Sghiatti

Sghiatti enrolled 124 patients, reported an unusually low number of adverse events, and was unavailable or refused attempts to conduct on-site monitoring visits until 04/08/02. When PPD finally conducted a monitoring visit, it discovered numerous discrepancies across the spectrum of study documentation, including no drug accountability log; dosing discrepancies; unreported adverse events; missing California informed consents for all 123 patients and the investigator failed to sign any case report forms or labs. In a series of e-mail and personal conversation(s), which occurred during the period 05/24/02 to 06/05/02 between PPD Project Manager Melinda Edwards and AVENTIS QA employee Ranjan Khosla, MD, AVENTIS was advised of the documentation problems at Sghiatti's site. However, in his final e-mail in the exchange, Khosla characterized the 5/28/02 conversation as "confirming that no doubt exists regarding the reliability of the data collected from this site, and no misconduct could be suspected" (Attachment 13).

PPD made a follow-up monitoring visit to Sghiatti's site in June 2002, during which progress was made on correcting documentation errors and numerous memos to file were created to acknowledge protocol violations. AVENTIS included data from 123 of Sghiatti's 124 enrolled patients in its study analysis (Clinical Study Report Table 2, pages 214-257, not attached).

5. Site #0881, Dr. Andrew Garner

Garner recruited a total of 95 patients and received a monitoring visit as a high enroller. By 01/18/02, AVENTIS had been informed that the monitoring visit had disclosed nearly two dozen missing, late or unsigned informed consents; the physician was himself a study subject, no source documentation relating to study treatment was maintained for any patient and other protocol violations (Attachment 14). The site was immediately closed to additional recruitment and an AVENTIS QA audit was performed thereafter, but all of the data produced by the site was ultimately used in the study analysis (Clinical Study Report Table 2, pages 214-257, not attached).

6. Site # 1654, Dr. Marie Monticciolo

Monticciolo enrolled and treated 27 patients in Study # 3014. A PPD monitoring visit on 02/27/02 disclosed suspected forgeries, nearly identical lab values between unique patients, frequent use of textbook normal vital signs across broad numbers of patients and very few adverse events were reported. AVENTIS QA declined to conduct an audit of the site and Dr. Monticciolo wrote two memos to file stating nothing was forged, lots of patients have normal vital signs, two patients happened to have nearly identical labs and the site promptly reports all adverse events (Attachment 15). AVENTIS QA accepted this resolution and Monticciolo's data were used in the final study analysis (Clinical Study Report Table 2, pages 214-257, not attached).

7. Site # 2557, Dr. Jeffrey McLeod

Although having never been an investigator in any previous study, McLeod enrolled 30 patients into Study # 3014. On 04/04/02, well after recruitment into the trial had ended, McLeod suggested in a telephone call with PPD that he had not had any of his patients sign the approved informed consent form. PPD reported the violation to AVENTIS QA, who directed PPD to immediately thank McLeod for "SPONTANEOUSLY REPORTING this major infraction" (emphasis in the original, twice) and conduct an immediate on-site monitoring visit. After retraining the site on informed consent procedures, a subsequent monitoring visit disclosed backdated signatures and dates on informed consent forms (Attachment 16). AVENTIS did not remove McLeod's data from its study analysis (Clinical Study Report Table 2, pages 214-257, not attached).

(AGENT'S NOTE: On 08/24/05, FDA served McLeod with, and McLeod agreed to, a Notice of Intention of Disqualification Proceedings and Opportunity to Explain (NIDPOE) letter for informed consent and protocol violations as well as submitting falsified information to AVENTIS regarding informed consent dates during his conduct of Study # 3014 (Attachment 17).)

8. Site # 2259, Dr. Samuel Stone

Dr. Stone enrolled and treated 24 patients during the course of Study #3014. Following an on-site monitoring visit, PPD notified AVENTIS on 01/31/02 that all 24 consent forms had problems, there were no source documents and the lab reports suggested there were no pre-therapy baseline labs obtained on any patient. AVENTIS QA conducted an audit one week later, correcting the informed consent issues

with new consents and a series of memos to file. No reference is made to the lack of baseline lab values in the patients, and the audit was closed on 6/13/02 (Attachment 18). AVENTIS used data from 23 of Stone's 24 enrolled patients in its final study analysis (Clinical Study Report Table 2, pages 214-257, not attached).

9. Site # 0096, Dr. Carl Lang

Lang enrolled a total of 251 patients into Study 3014, making him the second highest enrolling physician in the study. During an audit of 17 patients' source data on 02/19/02, AVENTIS QA employee Ranjan Khosla, MD, observed administrative and procedural irregularities in several informed consent forms; women of child bearing potential being enrolled without the required pregnancy tests; enrollment of patients with reported allergies to penicillin, and other protocol violations. Moreover, Lang and his study coordinator were not aware of the complete definitions of, or the reporting requirements for adverse events of special interest or serious adverse events (Attachment 19). Khosla was also aware that Lang moved his practice from Buffalo Grove, IL to Arlington Heights, IL halfway through the trial, though there is no report on whether or how Lang followed up on the study subjects from the previous location. Nonetheless, AVENTIS used all of Lang's data in its final study analysis (Clinical Study Report Table 2, pages 214-257, not attached).

(AGENT'S NOTE: Following the study's submission to the FDA, DSI conducted an inspection of Lang and found there was inadequate record keeping to ensure subject eligibility; the laboratory test results required at visit 1 and visit 2 were not obtained for 27 and 12 subjects, respectively.)

10. Site # 1622, Dr. William Terpstra

Terpstra enrolled and treated a total of 168 patients in Study # 3014. On 01/22/02, PPD notified AVENTIS QA that a recent monitoring visit revealed altered informed consent forms; Terpstra was unaware of GCP guidelines and IRB procedures; numerous patients had not returned for visit 2; inclusion/exclusion protocol violations existed in the few patients' charts that were available for monitoring and Terpstra did not appear interested in correcting any of these deficiencies. In response, AVENTIS QA directed that site be closed to new enrollments immediately and an interim monitoring visit be conducted (Attachment 20). A series of memos to file over the next two months were used to address the informed consent issues. There is no evidence that the missing visits were addressed, and AVENTIS used the data from 166 of Terpstra's 168 enrolled patients in its final study analysis (See Clinical Study Report Table 2, pages 214-257, not attached).

11. Site # 1129, Dr. Anne Kirkman-Campbell

Dr. Anne Kirkman-Campbell, a physician in Gadsden, AL, was recruited into the study on 10/31/01 as site # 1129 and quickly became the study's highest enrolling site. During her participation in the trial, she was visited four different times by approximately eight different monitors and auditors from PPD and AVENTIS (Attachment 21).

On 11/29/01, PPD employees Christine Hammond and Jerry Ferguson conducted the first monitoring visit of Kirkman-Campbell's site, by which time the physician had recruited 65 patients into the study. The monitors documented signature and date irregularities on informed consent forms; missing laboratory reports, inaccuracies in the drug log and the fact that the site's study coordinator was a patient. Kirkman-Campbell was instructed to prepare memos to file to address these deficiencies (Attachment 22). Many of the deficiencies and protocol violations were not fixed by the time of the next visit, an audit by AVENTIS QA (see below).

On 12/3/01, PPD Study Manager Roxann Evans e-mailed AVENTIS Study Manager Nadine Grethe and PPD Study Director Cathy Tropmann reporting that Kirkman-Campbell would enroll her 100th patient by the end of the day. Evans asked what the maximum number of subjects a single clinical investigator should be allowed to enroll. After consulting with statistician William Stager, Grethe informed Tropmann that each investigator could enroll as many as 500 study subjects (Attachment 23). Separately, Grethe wrote, "...I really hope he (sic) is a good site. Have we monitored him yet???? Do we have experience with him (sic) from a previous study?" (Attachment 24).

On 01/17-18/02, AVENTIS' Senior GCP QA Specialist Ranjan Khosla, MD, conducted an audit of Kirkman-Campbell's site and found more protocol violations involving informed consent signature and date irregularities; lack of pregnancy testing in women of child bearing potential; lack of familiarity with adverse events and their reporting, and other administrative irregularities (Attachment 25). Following this audit, Khosla sent Kirkman-Campbell a letter requesting the number of medical patients she saw in her practice for the three months she was involved in the study (Attachment 26). Kirkman-Campbell never provided this information.

Throughout the course of Study #3014, study meetings were conducted with PPD and AVENTIS personnel, and meeting minutes were maintained. A review of those meeting minutes disclosed that with respect to QA and monitoring entries, more entries related to Kirkman-Campbell than any other investigator. The first entry in the meeting minutes referring to Kirkman-Campbell was on 01/22/02, following an AVENTIS audit of her site. The entry simply stated, "Site Kirkman-Campbell - was a little uncomfortable with this site -- believes it requires additional monitoring. Would like approximately 25 patients monitored or 10% of patients -- sample patients from blocks of 50 patients (5 for each 50 patients). Additionally training for AESI also needed, however, no missing AESI detected during this visit" (Attachment 27, pg 4).

On 01/24/02, someone (NFI) from AVENTIS contacted PPD requesting information as to why Kirkman-Campbell drew extra blood draws from 19 patients. PPD employee Abigail Wear contacted the Kirkman-Campbell site telephonically, speaking to both Study Coordinator Michelle Snedecker and Kirkman-Campbell herself. Kirkman-Campbell blamed the extra blood draws on problems with the laboratory (Attachment 28).

On 01/29/02, after enrolling 407 patients, enrollment of new study subjects was closed at Kirkman-Campbell's site.

On 02/13/02, PPD Contract Safety Physician John Reynolds, MD, sent AVENTIS Study Manager Nadine Grethe an e-mail voicing his suspicions that a single clinical investigator, practicing with no sub-investigators, recruiting 407 patients into a study "will raise an eyebrow" (Attachment 29).

On 02/18 – 21/02, PPD Clinical Research Associates (CRAs) Ann Marie Cisneros, Beth Mills and Stephanie Love performed another audit of Kirkman-Campbell's site. They found, among other things, that 17 subjects had no history of the conditions required for inclusion; several subjects' charts were only two pages long; Subject #333's chart was altered in different ink; Subject #292 was not actually in the trial; Subject #405 was added to trial after being seen for back pain; a signature on Subject 249's informed consent appeared to be forged by the site's study coordinator (referred to subsequently as the "forged consent issue"); pregnancy tests were routinely not performed, and numerous informed consent issues across many patients. On the second day of the audit, Cisneros telephoned Khosla and her PPD superiors seeking advice on what to do about the 17 patients who had no history of bronchitis in their medical charts, but were participating in the trial to treat acute exacerbation of chronic bronchitis.

Khosla and her superiors at PPD informed Cisneros that the past medical history is not important. Copies of the audit notes were faxed to AVENTIS' Khosla on 2/21/02 (Attachment 30).

On 2/20/02, Reynolds completed an analysis of data from Kirkman-Campbell's site and found that a number of different patients had duplicative lab values, which suggested sample splitting. He also found that Kirkman-Campbell was the only clinical investigator audited who randomized numerous patients in rapid succession and during periods when the office was closed to patients. The construct of the trial required that patients be telephonically randomized while physically present during their first visit. Reynolds provided this information to PPD Study Director Cathy Tropmann (Reference is made to ROI #1, Attachment 1).

By 2/25/02, AVENTIS' study manager Nadine Grethe possessed Reynolds' findings concerning duplicative lab values and off-hour randomization of patients at the Kirkman-Campbell site. She forwarded them to AVENTIS' biostatistician, William Stager, who replied that he found nothing unusual in the data. Grethe e-mailed Stager's comments back to PPD, which caused Reynolds to renew his suspicions directly to Grethe in an e-mail later that day (Reference is made to ROI #1, Attachment 3).

On 02/26-27/02, PPD's Tropmann and Randall Anderson, from PPD's main office in Wilmington, NC, sought to have PPD's biostatistics department assist in "investigating some potentially fraudulent trends." Tropmann expressed concern that Stager wouldn't look at Reynolds' earlier findings.

On 2/27/02, PPD requested a teleconference with AVENTIS' Grethe and Khosla to discuss their concerns about Kirkman-Campbell's conduct as a clinical investigator. The first date Khosla was available was early the following week. In an internal AVENTIS e-mail later that night, Grethe told Khosla that they should talk about the Kirkman-Campbell site, but "could we please be careful how we disseminate information on this site until we do. By then we will also have Bill's [Stager's] final analysis on the lab values. I just don't want people panicking until there is a need to do so." (Reference is made to ROI #2, Attachment 6).

On 03/04/02, AVENTIS and PPD conducted a teleconference to discuss data irregularities at Kirkman-Campbell's site. According to various sources, the PPD attendees were Robert McCormick, VP, Quality Management Systems; John Reynolds, MD, Safety Physician Consultant; Jessica Lasley, Deputy Study Director; Roxann Evans, Study Project Manager; Melinda Edwards, CRA and Study Project Manager; and two of the CRAs (NFI) who participated in monitoring at Kirkman-Campbell's site. There is some disagreement as to whether Cathy Tropmann, PPD's Study Director, was present. For AVENTIS, sources indicate that Nadine Grethe, Study Manager; Michael Shoemaker, RPh, PhD, Head of Quality Assurance; Ranjan Khosla, MD, Senior GCP and Quality Assurance Specialist, and others (NFI) were present.

During interviews with OCI, several PPD employees refused to divulge the contents of the teleconference due to confidentiality agreements they signed covering PPD's work for AVENTIS. However, the reported upshot of the meeting was that AVENTIS would assume responsibility for monitoring the Kirkman-Campbell site.

In a briefing document submitted to FDA on 7/03/03, AVENTIS characterized the teleconference as undertaken "[i]n accordance with the applicable AVENTIS Global Regulatory SOP GREGU-QAC-PR-01-01 "Scientific Misconduct and Fraud"." The recommendations arising from the teleconference were that (a) William Stager was to perform a statistical analysis of Kirkman-Campbell's lab data, and (b) PPD was to send a follow-up letter to the site asking for written explanations to four of the most concerning issues: informed consent process; lack of source documentation; the rapid-fire

randomization of patients and the unusually low number of adverse events being reported. A follow-up meeting was to be held after reviewing the site's response to the follow-up letter and the outcome of Stager's analysis (Attachment # 31, pg. 2).

On 03/06/02, after reviewing a number of case report forms (CRFs) from clinical investigators across the spectrum of Study #3014, PPD CRA Sonia Pal e-mailed other PPD CRAs concerning her findings of CRFs arising from Kirkman-Campbell's site. She observed ink irregularities, no adverse events were reported for any of the first 360 patients and adverse events added post hoc and in different colored ink in the CRFs relating to patients 361-402 (Attachment 32).

On 3/14/02, Stager completed his analysis of laboratory data which arose from Kirkman-Campbell's site. According to a document AVENTIS provided to the FDA on 07/03/03, Stager concluded that the data from Kirkman-Campbell's site was similar to the data from the next two highest enrolling sites (Dr. Lang and Dr. Salerno), and therefore was not suspicious (Refer back to pgs 1 - 2 of Attachment 31; see also Attachment 33). These findings were similar to those which Reynolds himself came to, as identified in his 3/14/02 e-mail to four PPD CRAs and included the summary of his biostatistical analysis of data from Kirkman-Campbell's site which showed she reported a higher incidence of LFT changes than would be typical. Reynolds noted that similar findings were produced by data that were collected by Dr. Carl Lang at his site in suburban Chicago (Reference is made to ROI #1, Attachment 1).

On 3/19/02, a disagreement erupted between AVENTIS and PPD regarding whether the "forged consent issue" should be documented in a site follow-up letter from PPD to Kirkman-Campbell and the study file. AVENTIS did not want the matter included in the monitoring visit follow-up letter while senior PPD management disagreed. PPD's Robert McCormick instructed Cisneros to clearly document that AVENTIS required the removal from the follow-up letter" (Attachment 34). In the letter that PPD then issued to Kirkman-Campbell requiring her to correct deficiencies and violations found during the February 2002 monitoring visit, no reference was made to the suspected forged signature on Subject # 249's informed consent form (Attachment 35).

On 04/01/02 through 04/05/02, PPD conducted a combined interim and close-out monitoring visit at Kirkman-Campbell's site. PPD employees found more discrepancies, including the enrollment of patients with known allergies to antibiotics (Attachment 36). Following AVENTIS' recommendation, PPD addressed most of the protocol violations and informed consent problems with a blizzard of memos to file, 81 of which had been prepared by PPD employees on 3/26/02, to address shortcomings identified in the February 2002 monitoring visit. Another eight were prepared on 4/4/02 to address still-open findings from the November 2001 monitoring visit. Most of the memos to file simply acknowledged that the violations had occurred. No reference was made to the suspected forgery of Subject #249's informed consent form or in reply to Khosla's January 2002 query regarding how many patients Kirkman-Campbell saw at her practice during the months she participated in the study. The memos to file are voluminous and are not appended hereto.

During the period of 05/05/02 through 07/11/02, PPD employee Joyce Vito made numerous attempts to get Kirkman-Campbell to correct informed consent and other protocol violations throughout her study subject population. At the outset of this effort, AVENTIS QA's concern that patient # 249 - had a forged signature in the study file was raised for the first time to Kirkman-Campbell and a response was requested (Attachment 37). After repeated missed appointments and deadline extensions, Kirkman-Campbell still had not responded to PPD's pleas to rectify outstanding protocol violations and administrative deficiencies. The communications logs which document these attempts are voluminous and are not appended hereto.

On 05/22/02, AVENTIS locked its database for Study #3014. Included for analysis were all of the data from all of the clinical investigation sites referenced earlier in this report, including those from Kirkman-Campbell.

On 06/13/02, 22 days after database lock and three days after AVENTIS could address newly-found data, Reynolds sent an e-mail to Grethe identifying 34 patients who experienced elevated ALTs greater than eight times the upper limit of normal (8x ULN), and/or who experienced elevated ALTs 3x ULN and bilirubins greater than 1.5x ULN, both signals of an adverse event of special interest in the study (Attachment 38). One patient on the list was from Kirkman-Campbell's site. According to page 103 of the clinical study report, these data could not have been included in the final study database. Indeed, a review of Table 79 of the Clinical Study Report shows AVENTIS reported only eight patients experienced ALTs greater than 8x ULN and four patients experienced bilirubins greater than 1.5x ULN (Attachment 39).

On 07/11/02, Vito gave up trying to bring Kirkman-Campbell's site into compliance. At the direction of PPD Senior Project Manager Jean Noone, she documented her efforts to resolve outstanding issues at Kirkman-Campbell's site and notified Kirkman-Campbell that it was her responsibility to notify the IRB of the remaining protocol violations (Attachment 40). The validity of Patient # 249's signature was never resolved prior to AVENTIS' submission of Study #3014 to the FDA.

All of these problems notwithstanding, AVENTIS included Kirkman-Campbell's data in its final study analysis (See Clinical Study Report Table 2, pages 214-257, not attached). Had AVENTIS excluded Kirkman-Campbell's data, the firm would not have reached the agreed upon total of 12,000 patients randomized into the telithromycin arm (24,137 – 407 = 23,730, or, 12,159 telithromycin randomized patients – 204 telithromycin randomized patients from Kirkman-Campbell's site = 11,955).

THE SECOND SUBMISSION

On 07/24/02, AVENTIS submitted the final report for Study #3014 to the FDA as a part of the firm's complete response (Attachment 41) and NDA submission to the FDA's 6/1/01 approvable letter. Notable in the body of the 211-page clinical study report (CSR) was that AVENTIS represented that the trial had been conducted to good clinical practice (GCP) standards (CSR pgs 72-73, Attachment 42).

AVENTIS also represented in the CSR that protocol deviations were recorded in a total of 586 randomized patients (CSR pgs 106-107 and Table 8 at CSR pgs 275-8; collectively appended as Attachment 43). However, the reported protocol deviations did not include inclusion/exclusion criteria violations, such as women of child bearing potential not being tested for pregnancy before enrollment and allergies to beta-lactam and macrolide antibiotics, which were widely found in monitoring and audit visits. Moreover, a review of the source data verification at one location alone (Site # 1129, Kirkman-Campbell) revealed numerous patients with no history of bronchitis were enrolled for AECB. (AGENT'S NOTE: Reporting "those who entered the study even though they did not satisfy entry criteria" is the first example of a protocol deviation requiring reporting to regulatory authorities (See: ICH Guidance on Structure and Content of Clinical Study Reports E3, 11/30/95, pg 13; voluminous and not appended.)

From July 24, 2002, through early 2003, FDA's Division of Anti-Infective Drug Products (DAIDP) reviewed AVENTIS' second submission. From a safety standpoint, the review generally agreed with the firm regarding the adverse events (the executive summaries of the hepatic and biostatistical reviews are appended at Attachment 44 and 45, respectively). At the same time, DSI began its inspections of clinical sites which participated in Study #3014 and, as is reported below, began to uncover evidence that some of the highest-enrolling clinical sites produced data of questionable integrity.

In October 2002, FDA Consumer Safety Officers conducted a regulatory inspection of Kirkman-Campbell's site as a part of their inspection of Study #3014. The inspection was pre-announced, and Kirkman-Campbell notified AVENTIS it was going to happen. AVENTIS QA auditors Khosla and Michael Aschenbrenner, accompanied by PPD CRAs Beth Heding and Kim Reed, conducted an "Agency Inspection Preparation Visit" (Attachment 46). The FDA's subsequent inspection revealed so many indicators of fraud that the District issued a 483 and immediately referred Kirkman-Campbell to OCI for a criminal investigation. AVENTIS assisted Kirkman-Campbell respond to the 483.

From October 2002 through October 2003, OCI conducted its criminal investigation of Kirkman-Campbell, during which agents interviewed 220 of the 407 patients Kirkman-Campbell alleged were her study subjects in Study #3014. Of those 220 patients interviewed, 201 (91%) reported they did not participate in any trial. Three more didn't know whether they had been in a trial due to neurological debility. An additional 57 questionnaires sent to other reported study subjects were returned by the US Postal Service as undeliverable (Attachment 47).

On 12/19/02, DAIDP met with AVENTIS to discuss submissions for the upcoming AIDAC meeting. During that meeting, AVENTIS provided FDA with a voluminous briefing document to be provided to the AIDAC in advance of the scheduled meeting. A portion of that briefing document dealt specifically with Study 3014, and it contained nothing that suggested AVENTIS had any suspicions about the integrity of the study's data (Attachment 48). DAIDP took the opportunity to explain to AVENTIS that it had some concerns with data from at least two sites, Dr. Kirkman-Campbell's and Dr. Egisto Salerno's. AVENTIS stated that when they became aware of irregularities at Kirkman-Campbell's site, her participation was discontinued. They did not immediately address issues regarding Salerno, which received an FDA 483 earlier that day (Attachment 49).

A review of the transcripts made during the second AIDAC meeting, held 1/8/03, was conducted. After a brief recap of the earlier AIDAC meeting, AVENTIS representatives gave presentations about macrolide-resistant staphylococcus pneumoniae. They noted that Ketek, the first ever ketolide antibiotic (and thus representing an entirely new class of antibiotic) differs from macrolides in that it has the affinity to bind to two locations on the bacterial protein coat, making it more effective against bacteria when the macrolide receptor site has been deleted or mutated.

Thereafter, Dr. Paul Lagarenne gave a presentation on the safety profile of Ketek for AVENTIS. He opened and closed his presentation by stating that the most commonly identified adverse event was gastrointestinal distress. He recapped the experiences of the Phase III trials, during which hepatic, cardiac and visual signals were also detected. He then briefed the description and results of Study #3014, during which he said there were essentially no significant cardiac signals, incidence of elevated transaminases were consistent with comparator drugs, and identified blurred vision as an uncommon adverse event which occurred more frequently in patients randomized into the Ketek arm of the trial. Blurred vision was also dose-dependent.

With respect to hepatotoxicity, Lagarenne stated that approximately 1% of patients in Study #3014 experienced elevated liver function tests (LFTs) and that they were distributed approximately equally between patients receiving Ketek and those receiving the comparator drug, Augmentin. However, he said that ALT levels at or above eight times the upper limit of normal were uncommon, but numerically higher in the Ketek arm. Lagarenne drew attention to three Ketek patients had who experienced significantly elevated LFTs and two Augmentin patients who had similar adverse events. He said that four of the five were documented to have recovered fully and the fifth, an Augmentin patient, was lost to follow-up. Lagarenne said there were no reported cases of liver failure, transplant or chronic or

immune-mediated hepatic injury. He made no qualifying remarks about the reliability of the data or references to suspicions that some of the data were falsified.

Following his discussion of the results of Study #3014, Lagarenne presented data from European post-marketing adverse events reports. He said Ketek had been marketed in several European and South American countries since October 2001 and the data he provided the committee was from the period of October 2001 through December 2002. (AGENT'S NOTE: AVENTIS had previously provided the FDA with data only through October 2002.) He said approximately 1.5 million prescriptions had been written for Ketek in these countries, with nearly one million of them coming from Germany and France. With respect to these data, Lagarenne said, "To date, the post-marketing safety profile of telithromycin (Ketek) confirms the safety profile seen in clinical trials, with no new or unexpected safety signals identified." He attributed the one confirmed case of Torsades de Pointes to a non-drug related cause. He said that 64 adverse events of a hepatic nature were reported in 28 patients, including four patients who experienced cholestatic jaundice. One 75 year-old patient died of acute hepatitis A while on Ketek, but his medical history and course suggested the death was not drug-related.

In summarizing his presentation, Lagarenne said, "Thus, telithromycin's safety profile has been carefully evaluated in demonstrated in over 16,000 clinical trial patients and 1.5 million patients in the real-world setting."

In the brief question and answer period that followed AVENTIS' presentation, AIDAC member Dr. Ellen Wald questioned FDA officials at what point they observed a hepatitis safety signal in the post-marketing surveillance of Trovan, and Dr. Mark Goldberger replied that it was at about 1 million prescriptions written. Another committee member wanted more detail on the four cases of cholestatic jaundice, to which AVENTIS had Dr. James Lewis of Georgetown University respond. Dr. Lewis presented each of the four cases, concluding that for three of the cases, there wasn't enough information to conclude that the injury was drug related and, in one case, that the hepatic injury was probably due to the use of another concomitant drug.

The FDA then presented its materials to the committee. Dr. Charles Cooper recapped the Phase III trials excluding Study 3014, noting that AVENTIS submitted some additional controlled trials in its July 2002 submission. With a total of 4,472 patients receiving Ketek in Phase III trials, three had significant hepatic adverse events, two of which were "plausibly" related to the use of Ketek.

Dr. George Rochester then briefed the FDA's position with respect to Study 3014. He said 110 patients in one arm and 98 patients in the other arm (NFI) experienced ALTs above three times the upper limit of normal, and all but ten were followed up to clinical or laboratory recovery. Rochester said that while the hepatic adverse events were fairly evenly divided between Ketek and the comparator drug at lower ranges of toxicity, the numbers were less balanced when liver toxicities reached two or more times the upper limit of normal. He reported that across the LFTs, when toxicities reached seven to eight times the upper limit of normal, the distribution of adverse events was found consistently more frequently in patients dosed with Ketek than the Augmentin in ratios such as 35:22, 12:8 and 7:2 (at upwards of eight times the upper limits of normal). He presented three patients as case studies, all of whom eventually recovered, but all three of whom he thought (or the attending physician thought) were quite possibly experiencing toxicities related to the study medication.

Rochester said that the most surprising finding was that in Phase III trials, the reported adverse event rate was approximately 50% of patients, but in Study #3014, the number of patients experiencing adverse events was only 23% -- a drop of more than half. What made the information more peculiar was that Study #3014 had a much more robust population of at-risk patients and patients on

concomitant medications. He said, "A clinical trial still needs to have a little bit more structure [than a usual care setting practice]. So this was something that we did emphasize. In the actual carry out of the trial, this was certainly not a major thing that was emphasized." Rochester did not make any other comments regarding the suspected reliability of the data that arose from Study #3014.

After a hepatic pathologist briefed the committee that he also believed that both of the biopsies presented as parts of case studies were consistent with drug induced hepatotoxicity, Cooper returned to discuss the post-marketing surveillance data from Europe which AVENTIS provided to the FDA. He said during the period of October 2001 through October 1, 2002, approximately 900,000 prescriptions had been written in several countries, mostly in Germany and Italy. AVENTIS' later submission to the AIDAC included data through December 2002, by which time the marketing of Ketek had evolved to where the majority of the now 1.5 million prescriptions were written in Germany and France. Hence, the FDA evaluated information that was different than that which AVENTIS provided to the AIDAC. With respect to hepatic adverse events, Cooper noted that all 42 reported events originated from Germany. Two resulted in biopsies, and none resulted in death, liver failure or transplant.

During the following question and answer period, a committee member noted that the disparity between AVENTIS' presentation and the FDA's was so great that it was though they were listening to two different subjects. Cooper replied that some of the differences might be in interpreting the data, but he also noted that the company provided no post-marketing surveillance data from Italy, one of the countries in which a majority of the prescriptions were issued. When questioned about the drop of adverse event reporting from 50% in the Phase III trials to 23% in Study 3014, Rochester said that even given the variability with respect to indication (CAP versus all others), he "would have felt better about the vigilance probably in which these adverse events were collected" had the percentage been "something like 35 – 40 percent".

Thereafter, experts for AVENTIS and the FDA debated the interpretation of the biopsy slides, and a vote was taken. The AIDAC voted to recommend approval of Ketek for CAP, acute sinusitis and AECB, albeit with warnings about potential hepatic and visual adverse effects. Minutes of the meeting were not available for attachment.

On 01/21/03, DSI reported to DAIDP that its inspection of the three highest enrolling sites in Study #3014 uncovered significant issues at two of the three sites, and all three inspections resulted in the issuance of 483s. DSI recommended that the data from Kirkman-Campbell's site not be used in support of the NDA; some of the data from Lang's site might be acceptable for the NDA and Salerno's data could be used. It is of note that DSI had not yet received and analyzed the complete inspection reports for Lang and Salerno's sites (Attachment 50).

Instead of following the advisory committee's recommendation and approving Ketek, on 01/24/03, DAIDP issued a second "approvable letter" (Attachment 51), in which the agency notified AVENTIS that inspections at three sites revealed irregularities and/or violations of GCPs. In question 1.A.1., FDA asked AVENTIS to provide various study information "[i]n order to assess overall data integrity and to determine what role Study #3014 can have in support of your marketing application." It also asked for an analysis of adverse events reported in post-market surveillance from countries where telithromycin was already approved.

On 02/19/03, CDER held a Center Regulatory Briefing regarding Ketek involving the Directors and Deputy Directors of CDER, the Office of New Drugs, Office of Regulatory Policy, Office of Drug Safety, Offices of Drug Evaluation IV and II, numerous division directors and the director and staff from the Division of Anti-Infective Drug Products. The Division briefed that DSI's three inspections to date had

generated some concern about the integrity of Study #3014's date. The Division asked for recommendations regarding further assessment of data integrity for Study #3014, how the visual adverse event should be presented in the labeling and a recommendation regarding further assessment of hepatic risk. The committee recommended asking DSI to conduct more inspections to determine if Study #3014 can be used to support NDA and if it cannot, the Division might be able to rely upon foreign post-marketing data. With respect to the adverse events, the Center executives agreed with the Division that hepatic and cardiac adverse events appeared consistent with other currently marketed antibiotics, and Study #3014 did not appear to be critical to reaching this conclusion. Some in attendance suggested that the results of Study #3014 may not be critical for approval of Ketek for some of its proposed indications (Attachment 52).

On 02/28/03, DAIDP and AVENTIS met to discuss the approvable letter. In the minutes of the meeting, AVENTIS represented "that auditing of [t]he conduct of study # 3014 did not show significant deviations from good clinical practices (GCP)..." AVENTIS further represented that a review of three FDA 483s issued to clinical investigators involved in Study #3014 did not raise concerns about the conduct of the study. FDA represented that a review of the data was appropriate to ensure the data's integrity. After identifying what information the FDA would like to receive and in what order, the Agency advised AVENTIS that "If the integrity of the data for study #3014 cannot be assured, this study may not support the safety of telithromycin. In that case, the Division will have to rely on the post-marketing surveillance for the determination of the safety of the product and the proposed labeling" (Attachment 53). AVENTIS responded to the Agency's version of the meeting minutes several months later, stating "AVENTIS did have concerns about the conduct of Study # 3014 at the aforementioned sites and for the issues addressed in the 483 forms." The firm went on to say that given the study's design and facts known to AVENTIS, the firm "...did not believe the noted monitoring, auditing or 483 observations invalidated the data for the intended purpose of the study, i.e., assessing the safety of telithromycin" (Attachment 54).

On 3/6/03, the Director and others from the DAIDP met with the AIDAC in a closed (non-public) session. The director told the committee that the Division had not followed the committee's recommendation to approve Ketek because of DSI's initial findings with respect to the integrity of data AVENTIS provided in Study #3014. As of this writing, no meeting minutes have been located for this briefing because it was held in closed session.

On 07/03/03, AVENTIS submitted a briefing package to FDA entitled "Proposed Approach to Question 1.A.1," in which the firm sought to address the data integrity question the Agency asked in its 01/24/03 "approvable" letter. The cover letter said that the package contained essentially two things: a 74-page briefing document and reams of supporting documentation that provided information about the auditing and monitoring of the trial, and the results of a "five-site review" by Quantic Regulatory Services, LLC. The cover further made reference to a 49-site review performed by AVENTIS itself, but that wasn't included. The documents relevant to AVENTIS' and PPD's auditing and monitoring, where pertinent to this investigation, have been referenced earlier in this report. AVENTIS held Quantic out as a company with "expertise" in GCP evaluation, whose report would provide FDA with a roadmap to use in reviewing the voluminous submission as well as an assessment of overall GCP compliance, auditing and monitoring at the five sites.

A review of the fifty-page Quantic five-site review disclosed that AVENTIS and Quantic reviewed AVENTIS' and PPD's study documents associated with Lang's site; Salerno's site; Kirkman-Campbell's site; Dr. Zane Osborne's site; and Dr. Walter Gaman's site. The review process did not consider whether the data were collected under GCP standards, but rather in the "usual care" setting (emphasis in the original). The reviewers looked to see if the study documents for each site contained allegations or suspicions that a patient might not exist, didn't have one of the diseases indicated in the protocol,

didn't get the study drug, or that lab samples were drawn from patients other than the proper study subjects. They also looked for documentation that informed consent forms were missing or unsigned. Quantic and AVENTIS considered non-conformances found in these areas "may have significant impact on the acceptability of the study site or its data." Any other non-conformances, such as unreported adverse events, were noted as not having a significant impact on the acceptability of the study site or its data.

Quantic and AVENTIS found 91 non-conformances at Lang's site, though none that they considered impacted upon the acceptability of the study or its data. They found 61 non-conformances at Salerno's site, though none that they considered impacted upon the acceptability of the study or its data. They did not detect that Salerno, whose medical license was on probation at the time of the trial, was an unqualified investigator. Quantic and AVENTIS found eight non-conformances at Osborne's site, though none that they considered impacted upon the acceptability of the study or its data. They found another eight non-conformances at Gaman's site, though none that they considered impacted upon the acceptability of the study or its data. Gaman's site was reviewed because, following his participation in Study #3014, he received a NIDPOE from FDA for his conduct in an unrelated, earlier trial.

With respect to Kirkman-Campbell's site, the review found 156 non-conformances, four of which they considered could impact the acceptability of the study site or its data. The study documents contained one allegation that a patient did not exist, based on the monitor's assessment that the informed consent signature was probably a forgery. The review noted that the issue was subsequently reviewed by the AVENTIS Auditor (NFI), who "investigated and concluded that the subject received the proper consent." The study documents contained two allegations that study subjects did not have the indicated disease; the other 33 patients with no history of the disease in their medical records were resolved with memos to file or telephone calls to the monitor. Finally, there was one suspicion that some blood draws were not from the identified study subjects, based on Dr. John Reynolds' analysis at PPD. The review considered AVENTIS statistician William Stager's analysis, which found Kirkman-Campbell's labs similar to the next two highest enrollers, to sufficiently resolve that suspicion.

Quantic and AVENTIS then collectively formed a review board. The review board made the following statement regarding the data from each site except Kirkman-Campbell's: "It is recognized that that non-conformances were identified during the monitoring and auditing and/or disclosed in the documents reviewed. However, the Board has concluded that the non-conformances have been satisfactorily resolved and/or do not, individually or collectively, significantly compromise (i) the integrity of the study as conducted at this site or (ii) the reliability of the AESI data reported for this site. Accordingly, the Board has concluded that the AESI data are reliable." Each document is further qualified by saying that the Board's conclusions "...take into account the objectives of this primarily safety trial and the 'usual-care' setting in which it was conducted." The summaries are signed and dated by R. Owen Richards on 07/02/03. Richards added his title "President and Managing Director" of Quantic. Nowhere in the summary document does it represent that the study was conducted to GCP standards at any site, nor does it offer an assessment of overall GCP compliance, auditing and monitoring at the five sites.

With respect to Kirkman-Campbell, the review board found that the data produced at that site should not be used because, although the four allegation/suspicions were individually resolved, the overall number of non-conformances, uncooperative nature of the investigator and large number of lesser non-conformances that were not resolved made the review board conclude "that the integrity of the study as conducted at the site may have been significantly compromised, and the overall [adverse event of significant interest] data set submitted may not be complete."

An Internet search disclosed that R. Owen Richards is an attorney formerly employed as Vice President

of Worldwide Corporate Compliance and Associate General Counsel, Warner-Lambert Company. Quantic does not have an Internet website.

On 08/07/03, AVENTIS met again with FDA to discuss its proposed response to question 1.A.1., concerning the overall data integrity of Study #3014 in FDA's 01/24/03 approvable letter. The firm agreed to present experts' reports on the safety and efficacy of Ketek at a future date (which occurred on 10/20/03) and provide additional monitoring information from Study #3014. AVENTIS also updated FDA on a few adverse events that had not been captured in earlier presentations and on new information it uncovered regarding Dr. Keith Pierce (Attachment 55).

THE THIRD SUBMISSION

On 10/17/03, AVENTIS submitted its third major submission in the form of a complete response to the agency's 01/24/03 approvable letter (Attachment 56).

(AGENT'S NOTE: On 10/23/03, Kirkman-Campbell pleaded guilty to one count of mail fraud in relation to her submission of falsified clinical trial data to AVENTIS during Study #3014. For additional information relating to Kirkman-Campbell, refer to OCI case file

On 3/25/04, DSI provided DAIDP with a consult following eight inspections associated with Study #3014. DSI found that AVENTIS' best efforts at monitoring failed to detect data integrity problems when they clearly existed. For example, DSI found that data from the following five sites, accounting for a total of 961 patients, should be excluded from consideration for the NDA because of "non-compliance with FDA regulations and multiple instances of fraud":

Site # 1057, Dr. Egisto Salerno, 171 patients (Unqualified; probated medical license)
Site # 1129, Dr. Anne Kirkman-Campbell, 407 patients
Site # 0759, Dr. Manjeet Kaur Achreja, 116 patients
Site # 1892, Dr. James Knecht, 99 patients
Site # 0965, Dr. Rashid Khan, 168 patients

DSI concluded that "...the integrity of data from all sites involved in Study 3014 cannot be assured with any degree of confidence" (Attachment 57).

On 03/31/04, FDA's DAIDP finished its medical review of AVENTIS' third submission for Ketek, only the summary and introduction of which are appended at Attachment 58. Of particular note is the fact that the safety review is primarily based upon post-marketing data and, for the first time, a safety signal is observed with respect to myasthenia gravis exacerbation. This signal was found in the foreign post-marketing data (Attachment 59), not in any previously conducted clinical trials.

On 4/1/04, FDA issued its approval to AVENTIS to market Ketek (Attachment 60). The approved labeling contained a paragraph under the WARNINGS header which discussed the potential for myasthenia gravis exacerbations.

Prior to a third AIDAC meeting, two labeling changes were made owing to increased risk. On 11/2/05, a labeling change was approved which called attention to the increased risk of syncope. On 6/29/06, a labeling change was approved that heightened the warnings concerning hepatotoxicity and myasthenia gravis.

On 12/14/06, a two-day joint meeting of the Anti-Infective Drug Advisory Committee and Drug Safety

and Risk Management Advisory Committee began to discuss the overall benefit to risk considerations for Ketek. At the outset, DAIDP asked the committees to provide FDA with recommendations as to (1) whether Ketek should continue to be marketed for each of its approved indications, and if so, (2) should its marketing be limited or restricted.

In recapping the regulatory history of Ketek's NDA, Dr. Janice Soreth, DAIDP Director, recounted how evidence accumulated from just prior to the second AIDAC meeting in January 2003 through DSI's written consult in March 2004 that Study #3014's data lacked integrity. She said the consult "concluded that monitoring of study sites by the sponsor failed to detect problems found by FDA inspections when they clearly existed. Hence, the integrity of data from all 1,800 investigative sites (sic) in that study could not be assured with any degree of confidence and we did not rely on those data to take regulatory action." Soreth then went on to very specifically list what trials and data the Division did rely upon in approving Ketek for marketing.

The joint committee then heard data from both FDA and the sponsor (now SANOFI-AVENTIS) which was produced by a variety of analyses of post-marketing data, both domestic and ex-US. These data essentially revealed that Ketek's hepatotoxicity signal was similar to slightly higher than other antibiotics, but less than half of what was observed with Trovan. Ketek had strong syncope and visual signals, but cardiac signals milder than similar antibiotics. Finally, adverse events secondary to telithromycin use seemed to be more prevalent in female patients than males.

On behalf of the sponsor, Dr. James Lewis, a hepatologist from Georgetown University, presented his analysis of the three North Carolina cases reported in or about May 2005. He said the first patient, a male, had self-resolving elevated LFTs for approximately eight weeks with no sequellae. Another female had subfulminant acute liver failure, resulting in a transplant. Doctors noted she had some confounding signs suggestive of an autoimmune disease, but admitted they would never know for certain what the cause of her liver failure was. The third patient, a male, complained of weakness, nosebleeds, nausea, bloody vomitus and right-sided belly pain for two months prior to presenting at the emergency room and six weeks before being exposed to telithromycin. He died of cardiopulmonary arrest shortly after admission to the hospital. An autopsy revealed lymphocytic infiltrate in the liver which, according to Dr. Lewis, actually made a hypersensitivity reaction less likely. His liver was found to be twice the normal size and his spleen was three times the normal size. A subsequent pathology report also detailed viral myocarditis. Dr. Lewis concluded that while Ketek may have exacerbated this patient's condition, it could not have initiated it.

On the second day of the joint committee hearing, the committees debated using inferiority testing versus superiority testing as the proper methodology to re-evaluate Ketek's efficacy. Noting that AECB and AS were typically self-resolving disease processes, efficacy testing in 2006 was now different than was required in 2003. Because the NDA's existing efficacy testing had been accomplished to the old standard, the committee discussed whether using the new criteria would identify the same benefit ratio for each of Ketek's approved indications.

Following the discussions about efficacy testing, Dr. Rosemary Johann-Liang, CDER Division of Drug Risk Evaluation, summarized the hearing's risk to benefit considerations. In recounting safety (risk) data available, she stated, "Occasionally, we are fortunate to be able to test a safety question in a randomized and controlled large safety trial such as Study #3014. Study #3014 was set up to look at Ketek versus Augmentin in a comparative, prospective manner. Unfortunately, as you have heard, the results of the study are not usable. Thus, we are left with uncertain measures and opinions about how to resolve the uncertain totality of evidence of harm."

During the public presentation portion of the hearing, Dr. David Ross, a medical reviewer of the original Ketek NDA, made a series of allegations against the FDA and AVENTIS. Essentially, he alleged that, "...there was substantial evidence of fraud in this application. AVENTIS knew there were problems but did not tell the FDA. FDA managers knew but failed to tell this committee. FDA managers used the same data to approve Ketek despite warnings from criminal investigators and reviewers about suspected systematic fraud." A copy of Ross' slide presentation, with his printed statement in the notes, is appended at Attachment 61.

Prior to the discussion and voting, both the sponsor and the FDA were given an opportunity for closing comments. Richard Gerrell, Global Head of Regulatory Affairs Development, SANOFI-AVENTIS, made the following statement: "...We have heard, over the last two days, some characterizations of Study #3014. We strongly object to the characterization that the company turned a blind eye or coaxed investigators or, even worse yet, induced them to conduct fraud in the support of one of our studies. This is simply false. We acted in good faith in the conduct of Study #3014. First, we did not ignore, we did not coax and we did not do anything unethical with our investigators. We do seek, as part of our routine good clinical practices to exclude such investigators from our studies. As the court found in the sentencing of the one investigator in question, that this investigator committed "sophisticated fraud" to perpetuate her fraud against AVENTIS, the FDA and the public. At the time of the second advisory committee meeting, we believed that the GCP violations and deviations had been conducted at this one study investigational site were to be remediated and that the data was going to be satisfactory. It is important to note that the tools that we have at our disposal as a sponsor are different than the tools that the FDA and the Criminal Investigation Branch has at their disposal to detect fraud. To this point, we trust that the FDA and the Criminal Investigations Unit are continuing to do their investigations of Study #3014." Gerrell went on to reaffirm that SANOFI-AVENTIS places great importance on patient safety.

When the FDA took its turn with final comments, Dr. Joanne Rhoads, who was the director of DSI during the period of the Ketek NDA review, told the committees that usual care trials were difficult to do, to monitor and to inspect. She said that this type of trial necessarily uses inexperienced clinicians and that even experienced monitors often don't find existing fraud. She then stated, "But, considering the nature of the trial and the extent of the problem, we did not see direct evidence that this information was ignored by the company." Rhoads told the committees that after inspecting three sites and finding significant issues at all three, DSI referred all three investigators to OCI. In recapping the findings of all eight sites eventually inspected by DSI, Rhoads said the overall issue was that the data at each site could not be verified. She then repeated, "That doesn't mean that we found adverse events specifically that hadn't been reported. It was sloppiness. It was [we] couldn't verify subjects when they came, if they were there. There were lots of problems that seemed sufficient to say, we can't rely on this information." Rhoads went on to explain how confidentiality policies and rules within the Agency had an impact on what could be told to the second advisory committee. When asked by a committee member whether there was an attempt on the part of the company to somehow hide or continue with the fraud, Rhoads said "I think the main points are that we did not find deliberate hiding of serious adverse events... We just don't know what the quality of the information is."

At the conclusion of the discussion period, during which no further reference to Study #3014 was made, the committee voted to recommend the FDA restrict Ketek's marketing to the sole indication of community acquired pneumonia and require a black-box warning (Attachment 62).

On 2/12/07, FDA approved a labeling change for Ketek which added a black-box warning making myasthenia gravis an absolute contraindication, heightened warnings about hepatotoxicity and syncope, and listed its only indicated use as community acquired pneumonia.